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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,778	04/14/2006	Tetsuo Ikezono	P26460	9010

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GREENBLUM & BERNSTEIN, P.L.C.
1950 ROLAND CLARKE PLACE
RESTON, VA 20191

EXAMINER
FOSTER, CHRISTINE E

ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
04/29/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

gbpatent@gbpatent.com
pto@gbpatent.com

Office Action Summary	Application No.	Applicant(s)	
	10/517,778	IKEZONO ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *8-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment, filed 1/30/2009, is acknowledged and has been entered. Claims 1, 3, and 6 were amended. Claims 1-13 are pending in the application, with claims 8-13 currently withdrawn. Accordingly, claims 1-7 are currently pending and subject to examination below in light of the elected species of SEQ ID NO:7.

Priority

2. The present application is a proper National Stage (371) entry of PCT Application No. PCT/JP03/08123, filed 06/26/2003. Acknowledgment is also made of Applicant's claim to priority under 35 U.S.C. 119(a)-(d) to Application No. 2002-187479, filed on 06/27/2002 in Japan.

Objections/ Rejections Withdrawn

3. The objection to the specification has been obviated by Applicant's amendments thereto.

4. The objection to claim 3 has been withdrawn.

5. The rejections under § 112, 2nd paragraph not reiterated below have been withdrawn.

Claim Objections

6. Claim 1 is objected to because of the following informalities:

The preamble of claim 1 recites a method "for detecting a perilymph fistula"; however the body of the claim concludes with the step of "using the detected existence of Cochlin as an

indicator of the possibility of a perilymph fistula". It is suggested that the claim be amended so that the preamble corresponds with the method steps recited in the body of the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 3 recites "an **N-terminal fragment** of a p63, p44, or p40 isoform of Cochlin, or a 16kDa **N-terminal fragment** of Cochlin"" in line 3. The terminology "N-terminal fragment" renders scope of the claim unclear because an "N-terminal fragment" might refer to the N-terminal amino acid of a protein, to the N-terminal half of the protein, or to various N-terminal portions thereof. As such, the reference to an "N-terminal fragment" is ambiguous because no specific or limiting definition for this term has been provided in the instant specification. Furthermore, different researchers may define domain boundaries differently. For all of these reasons, the metes and bounds of the claim are unclear because it is not apparent what portion or portions of Cochlin would be considered to represent "the N-terminal fragment".

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ikezono et al. (Biochimica et Biophysica Acta 1535 (2001) 258-265) in view of the Dictionary of Medicine, definition for the term "perilymph" (2000); Peter Collin Publishing, London: Peter Collin Publishing. Retrieved October 21, 2008, from http://www.credoreference.com/entry/1051726/), Magal et al. (US 6,274,554 B1), Wall et al. ("Perilymph fistula pathophysiology" Otolaryngol Head Neck Surg. 1995 Jan;112(1):145-53), and Botstein et al. (US 6,913,919 B2).

Ikezono et al. teach a method for detecting the protein product of the *Coch* gene (i.e., Cochlin) in homogenized inner ear tissue samples (see in particular the abstract; page 259, section 2.1; and page 264, right column, penultimate paragraph).

The reference differs from the claimed invention in that it fails to specifically teach detection of Cochlin in a body fluid existing in the middle ear.

The Examiner finds the following facts:

The Dictionary of Medicine teaches that perilymph was fluid known to exist in the labyrinth of the inner ear.

Magal et al. discusses physiology of the inner ear and teaches that proteins penetrate the membrane of the round window into the perilymph of the inner ear (column 20, lines 45-48).

Wall et al. relates to the pathophysiology of perilymph fistula, which is an abnormal communication between the inner and middle ear cavities that results in leakage of perilymph from the inner ear into the middle ear (page 145, abstract and left column). The reference teaches that diagnostic methods are emerging for the detection of perilymph fistula, based on detection of a marker that has passed from the inner ear space (where perilymph is normally found) to the middle ear space (page 147, paragraph bridging the left and right columns; and page 148, paragraph bridging left and right columns). Such perilymph markers can be endogenous substances that are unique to perilymph or cerebrospinal fluid but absent in serum (page 149, "Perilymph Markers"). In other words, proteins that are specific to perilymph can be used as markers to detect leakage of perilymph into the middle ear. Wall et al. teach that such markers include β2-Transferrin, which can be detected by gel-electrophoresis and immunoblotting (abstract and page 149).

Botstein et al. teaches that Cochlin (Coch-B2) is specifically expressed in the inner ear. See column 12, line 60 to column 13, line 10.

From the teachings of The Dictionary of Medicine that the labyrinth of the inner contains perilymph, there is a strong basis to believe that the inner ear tissue samples studied by Ikezono et al. contained perilymph, as these tissue samples included the inner ear labyrinths (see Ikezono et al. page 264, right column, penultimate paragraph).

Furthermore, although Ikezono et al. detected Cochlin in the homogenized tissue samples and did not separately analyze the perilymph component therein for the presence of Cochlin, one of ordinary skill in the art would reasonably expect this protein to be found in perilymph because Magal et al. taught that proteins penetrate into the perilymph. As an inner ear protein, one of ordinary skill in the art would reasonably expect Cochlin to exist in perilymph.

Therefore, from the teachings of Ikezono et al., the Dictionary of Medicine, and Magal et al., it would have been obvious to one of ordinary skill in the art to conclude that the protein Cochlin is found in perilymph.

In addition, in view of the teachings of Wall et al. and Botstein et al., it would have been further obvious to one of ordinary skill in the art to detect Cochlin as a perilymph marker in fluid in the middle ear. One would have been motivated to do this in order to detect perilymph fistula. In particular, Wall et al. taught that endogenous substances that are found in perilymph but absent in serum can be used as perilymph markers in order to detect perilymph fistula (i.e., leakage of perilymph from the inner to the middle ear). Botstein et al. teaches that Cochlin was known to be specific to the inner ear. Consequently, one of ordinary skill in the art would reasonably expect Cochlin not only to be expressed in perilymph as discussed above, but also to be specific to the inner ear and not also expressed in serum, for example.

In summary, it would have been obvious to one of ordinary skill in the art to recognize Cochlin as a specific perilymph marker according to the criteria taught by Wall et al., and to detect this protein in middle ear fluid in order to detect perilymph fistula (as taught by Wall et al.).

With respect to claim 3, Ikezono et al. teach that Cochlin exists in the inner ear as different isoforms, identified as p63, p44, and p40. p63 is the most amino terminal portion of Cochlin (see page 264, left column; and also Tables 1-3 and Figure 4). Therefore, because multiple Cochlin isoforms were known in the art to exist in the inner ear, including the N-terminal Cochlin fragment p63, it would have been further obvious to detect this isoform of Cochlin when analyzing middle ear fluid for the presence of Cochlin. The selection of one of a finite number of known isoforms would have been obvious.

With respect to claim 4, Wall et al. teaches detection of the perilymph marker β2-Transferrin by gel-electrophoresis and immunoblotting (abstract and page 149). Given that such methods were known in the art to be suitable for detecting perilymph markers, it would have been obvious to select such known immunological methods detect Cochlin as a perilymph marker.

4. Claims 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ikezono et al. in view of the Dictionary of Medicine, Magal et al., Wall et al., and Botstein et al. as applied to claim 1 above, and further in view of Robertson et al. (Human Molecular Genetics 2001, Vol. 10, page 2493-2500), the Academic Press Dictionary of Science and Technology (definition for the term "polyclonal"; Oxford: Elsevier Science & Technology (1996); retrieved October 22,

2008, from http://www.credoreference.com/entry/3144515/) and Wolfe, S.L., (Molecular and Cellular Biology, 1993, pages 790-793).

The references are as discussed above, which teach methods for detecting Cochlin substantially as claimed. Ikezono et al. teaches p63, a N-terminal fragment of Cochlin. Wall et al. teaches immunoblotting procedures to detect perilymph markers. However, the references fail to specifically teach detecting of Cochlin using an anti-Cochlin N-terminal fragment antibody.

Robertson et al. teach methods for detecting the human protein cochlin using a polyclonal antibody raised against the N-terminal 135 residues of cochlin (abstract and pages 2495 and 2498-2499, the sections entitled "Generation of antibody against cochlin").

It would have been obvious to employ the anti-Cochlin N-terminal fragment antibody of Robertson et al. to detect Cochlin in middle ear fluid as a marker of perilymph fistula in the method of Ikezono et al., the Dictionary of Medicine, Magal et al., Wall et al., and Botstein et al. because the selection of a known material for its known purpose would have been obvious. One would have had a reasonable expectation of success because Robertson et al. taught that the antibody successfully detected Cochlin in biological samples.

With respect to claim 6, the polyclonal antibody of Robertson et al. was raised against a peptide sequence corresponding to amino acid residues 27-161 of human cochlin (see Figure 1B and legend). The Examiner notes that SEQ ID NO:1 is the amino acid sequence of human cochlin as disclosed instantly. Although Robertson et al. teach an antibody that recognizes an epitope within residues 27-161, and do not specifically mention residues 36-127, the reference nonetheless reads on the claim for the following reasons.

It was well known in the art that polyclonal sera comprises a mixture of antibodies of different specificities directed toward multiple antigenic determinants present on a particular antigen. See the Academic Press Dictionary of Science and Technology, which defines a polyclonal antibody as a population of heterogeneous antibodies derived from multiple clones, each of which is specific for one of a number of determinants found on an antigen.

In addition, Wolfe discloses that the size of an epitope (i.e., antigenic determinant) bound by an antibody is between 3 to 16 amino acids in length (see particularly the bottom of the left column of page 791). As such, there is a strong scientific basis to believe that the polyclonal antibody directed against amino acids 27-161 of human cochlin would necessarily recognize antigenic determinant within amino acids 36-127 of this protein, given that these two sequences share numerous antigenic determinants.

With respect to claim 7, the Examiner notes that the claims employ open transitional language ("having"). In other words, the antibody recognizes an antigenic determinant found in a polypeptide that includes the amino acid sequence of SEQ ID NO:7, but the polypeptide may include additional amino acid residues on either end of SEQ ID NO:7. The claims therefore read on an antibody that recognizes an epitope found within the full-length Cochlin protein, for example.

The antibody of Robertson et al. was raised against a peptide sequence corresponding to amino acid residues 27-161 of human cochlin (see Figure 1B and legend). As disclosed instantly, SEQ ID NO:7 corresponds to amino acid residues 114-127 of human cochlin. Therefore, in teaching an antibody that recognizes an epitope within amino acid residues 27-161 of human

cochlin, the reference reads on an antibody that recognizes an epitope within a protein that includes amino acid residues 114-127 of cochlin (i.e., SEQ ID NO:7).

In addition, because the polyclonal antibody of Robertson et al. includes a mixture of antibodies of different specificities directed toward multiple antigenic determinants present on a particular antigen, there is a strong scientific basis to believe that the antibody would necessarily recognize epitopes contained within amino acids 114-127 of cochlin, given that this sequence shares numerous epitopes in common with the larger sequence defined by residues 27-161.

Response to Arguments

10. Applicant's arguments filed 1/30/2009 have been fully considered.

11. With respect to the rejection of claim 3 under § 112, 2nd paragraph, Applicant does not specifically traverse the grounds on which the objection was made but points to the instant amendment (Reply, page 8). This is not found persuasive because the claim continues to recite the terminology "N-terminal fragment," which renders the scope of the claim unclear for reasons of record as set forth above.

12. With respect to the rejections of claims 1-4 under § 103, Applicant's arguments (Reply, pages 8-11) have been fully considered but are not persuasive.

Applicant argues that none of the cited documents teach that Cochlin is unique to perilymph or cerebrospinal fluid but absent from serum (Reply, page 9, last paragraph to page 10, second paragraph).

This is not found persuasive because as discussed above, Botstein et al. taught that Cochlin is *specifically expressed* in the inner ear. From this, one of ordinary skill in the art would understand that Cochlin is specific to the inner ear as compared to serum, for example.

The Examiner agrees that none of the cited references provide definitive data to show that Cochlin is found only in perilymph and is completely absent in other body fluids, but does not agree that a determination of obviousness would require such a rigorous standard. Although Wall mentions the desire for markers that are "unique" to perilymph but "absent" in serum, rare indeed is the biomarker that would possess 100% specificity. One of ordinary skill in the art would understand that a specific marker of perilymph need not exhibit complete absence of expression in any other fluid or tissue. It was known that Cochlin was specific to the inner ear; consequently, the fact that it was not apparently known that Cochlin was 100% specific to the inner ear is not found persuasive evidence of non-obviousness.

Furthermore, it is noted that the claims do not require positive or definitive determination of perilymph fistula based on Cochlin detection alone. Rather, the claims recite "using the detected existence of Cochlin **as an indicator of the possibility of a perilymph fistula**".

In addition, obviousness does not require absolute predictability of success--all that is required is a reasonable expectation of success. The appropriate question is not whether one of ordinary skill in the art would expect less than 100% accurate results in detecting Cochlin to diagnose perilymph fistula, but rather, whether one of ordinary skill in the art would still reasonably expect Cochlin to be a "indicator" of "possible" perilymph fistula even notwithstanding the possibility of a certain level of false positive or false negative results due to some level non-specific expression of Cochlin in other fluids or tissues other than perilymph.

Applicant further argues that Botstein teaches that "Cochlin is expressed in the inner ear, i.e., the cochlea - not the perilymph" (Reply, page 10, second paragraph). This is not found persuasive because as evidenced by The Dictionary of Medicine, the perilymph is part of the inner ear. Therefore, the Examiner finds insufficient evidence to support the position that "inner ear" would refer only to "cochlea" and exclude "perilymph".

Applicant further argues that Magal appears to disclose that proteins are capable of penetrating into the perilymph when accompanied by a suitable vehicle and/or agent (Reply, page 10, last paragraph). As best understood, Applicant does not dispute that proteins penetrate into the perilymph but argues that it is possible to interpret Magal as meaning that proteins are only capable of doing so when formulated with a suitable vehicle such as microspheres or liposomes. The Examiner does not agree with this interpretation of the reference and finds that the statement "it has been shown that proteins do penetrate the membrane of the round window into the perilymph of the inner ear" is not qualified in this manner. Furthermore, from the reference to "slow or sustained release", it is believed that one of ordinary skill in the art would understand that the role of the microspheres or liposomes disclosed by Magal et al. is to allow for gradual release of protein and not for penetration into the perilymph. In addition, there is additional evidence of record indicating that proteins were known to be present in perilymph (in addition to Wall et al. (discussed above), see also for example Rauch et al. (Applicant's IDS of 8/15/2005, especially at page 549, right column, last paragraph). Therefore, even notwithstanding the teachings of Magal et al., it is maintained that one of ordinary skill in the art would reasonably expect to find proteins in perilymph.

Applicant further argues that it is not possible to argue that Cochlin expression is both unique to perilymph or cerebrospinal fluid, but absent from serum, AND that one of ordinary skill in the art would expect to find Cochlin in the perilymph as a result of leakage from surrounding tissue (Reply, page 11, first paragraph).

This is not found persuasive because as discussed above, the Office does not contend that the prior art provides definitive data to show that Cochlin is found only in perilymph and is completely absent in other body fluids or tissues. Even if one might not expect Cochlin to be exclusive to perilymph, it is maintained for reasons of record that one would reasonably expect success in using this protein as an indicator of the possibility of the presence of perilymph. Moreover, the Office has not contended that one would expect Cochlin to be found in perilymph due to any one particular mechanism. Nonetheless, because Cochlin was recognized to be a protein specific to the inner ear and was found in samples containing inner ear fluid (perilymph), and when taken together with the knowledge in the art that proteins are present in perilymph (as taught by Magal et al. and Wall et al.), it is maintained that one would reasonably expect that Cochlin would be present in perilymph.

Applicant does not separately argue the limitations of dependent claims 4-7 (see Reply, pages 11-12).

Conclusion

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/Christopher L. Chin/
Primary Examiner, Art Unit 1641